Thrombolysis for acute ischemic stroke: still a treatment for the few by the few

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The National Institute of Neurological Disorders and Stroke (NINDS) trial was groundbreaking.[1] It demonstrated that stroke patients could be admitted to hospital, scanned, and treated within 3 hours of stroke, a major achievement in the early 1990s. The Food and Drug Administration accepted the NINDS evidence (actually conducted as 2 consecutive trials, only 1 of which gave positive results) and licensed recombinant tissue plasminogen activator (tPA) for the treatment of stroke.

That was 1995, and stroke trial methods have moved on, particularly in randomization and follow-up methods. Patients were randomly allocated into the NINDS trial by the selection of a drug "prepack" stored in each center, followed by retrospective notification to the central trial office within 2 hours. Thus, it was impossible to balance randomization for baseline factors such as stroke severity. The 3-month follow-up was by a physician in each center. It is difficult to know how blind this assessor truly was (the biologic effects of recombinant tPA are difficult to blind). The opportunity *not* to be blind to treatment allocation was obvious. Modern trials commonly use prospective randomization from a central site and minimization (a method of balancing important prognostic variables across treatment and control groups) to avoid imbalances in baseline patient characteristics and improve security (ie, once in the trial, the patient cannot be omitted). The use of central telephone or postal follow-up directly to the patient can also avoid any potential for local investigator influence.

Could this dated design have influenced the NINDS results? Jeffrey Mann's article is an important comment and a careful piece of detective work that clearly describes the imbalance in stroke severity between patients allocated to receive tPA and those given placebo. But how important is this imbalance? We have independently examined the published data from the NINDS investigators and agree that the baseline imbalances explain about a third of the apparent benefits. The baseline imbalance alone would produce the following proportion of excellent outcomes without the tPA: 0 to 90-minute group, 32% tPA versus 33% placebo; 91 to 180-minute group, 39% tPA versus 32% placebo; and all patients randomly allocated into the trial, 0 to 180 minutes, 36% tPA versus 32% placebo. This 4% absolute difference, or 40 per 1,000 more independent survivors, arose simply because of a chance imbalance in baseline stroke severity and has been overlooked by neurologists. False-positive results are common in small, inevitably unbalanced, trials. The warning, "Don't Ignore Chance Effects" (or DICE) is an excellent example of how chance skews trial results, and it should be more widely recognized.[2]

Does this mean that the NINDS result is invalid? No, for two reasons. First, of the 120 per 1,000 more who were alive and independent according to the NINDS trial, in theory, 80 per 1,000 had improved outcome that might be attributed to the use of the recombinant tPA, not chance. Second, the result is consistent with the data from patients randomly assigned within 3 hours in the other seven trials of tPA.[3] In fact, the NINDS trial contributes only 21% of the total data available on tPA (8 trials, total of 2,955 patients, up to 6 hours after stroke). Given the citation bias of the positive NINDS trial (43 articles, equivalent to 6% of the sample size, or 14 patients per publication!), it is easy to understand why this has been overlooked.

The totality of the data suggests that tPA is doing something, but the key question, and the factor that above all else may have kept tPA from wider use, is how big is that effect and in which patients? The big disappointment is that the uncritical and optimistic acceptance of tPA has discouraged the stroke community from obtaining more convincing data and actually blocked the finding of safe ways to give tPA more widely. If tPA is so effective, then it should be available for most people, not just the few lucky enough to be admitted to a specialist tertiary referral center. Patients with stroke are often elderly, frail, and aphasic and thus unable to fight for their rights. This simple fact is reflected in a grossly disproportionate lack of interest, research funding, and medical intervention for stroke compared with far less devastating conditions.[4]

So, 6 years after NINDS, thrombolysis remains a treatment for the few by the few. How can the stroke community solve this problem? First, implement basic proven knowledge: organize inpatient stroke services, and give aspirin immediately to all aspirin-eligible patients. Then, where information is lacking, get more data: for those patients for whom the use of tPA may be promising but is unproved, we suggest randomly allocating them into a trial such as the Third International Stroke Trial, which is evaluating the use of tPA up to 6 hours after definite stroke onset. Details are available from the authors or at the trial's web site (www.dcn.ed.ac.uk/ist3).

Competing interests: Dr Lindley has received an unrestricted educational grant from Boehringer Ingelheim, who holds the license for tPA in Europe. He edits a national mulidisciplinary newsletter sponsored by Boehringer Ingelheim. As editor, he receives sponsorship to attend the European Stroke Conference each year. Professor Wardlaw is the director of the SHEFC Brain Imaging Research Centre for Scotland, which received 3% of its set-up support from Boehringer Ingelheim as part of a government and Medical Research Council-sponsored joint research initiative. Dr Lewis has no potential financial conflicts of interest. However, all of the authors are actively engaged in gathering more data on the use of tPA in stroke and so are running the Third International Stroke Trial, in which all data collection, storage, analysis, and publication are by a collaborative group of stroke-interested trialists, independent of industry. We welcome interested centers.

References

1 National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;333:1581-1587.

2 Counsell CE, Clarke MJ, Slattery J, Sandercock PA. The miracle of DICE therapy for acute stroke: fact or fictional product of subgroup analysis? *BMJ* 1994;309:1677-1681.

3 Wardlaw JM, del Zoppo G, Yamaguchi T. Thrombolysis for ischaemic stroke (Cochrane Review). *Cochrane Library.* Oxford, UK: Update Software; 2001.

4 Rothwell PM. The high cost of not funding stroke research: a comparison with heart disease and cancer. *Lancet* 2001;357:1612-1616.

In response to our "Any questions?" box, a reader from France asked:

Is it necessary to admit patients with acute pericarditis diagnosed in the emergency department when the patient seems ("seems": ouch!) to have idiopathic or viral pericarditis, has no dysrythmia, no tamponade, is clinically stable with no alarming sign or symptom, has controlled pain, and is socially and intellectually fit for ambulatory treatment and follow-up?

A major cardiology textbook, although written in the English language by experts west of Europe, states, "Treatment aims to relieve symptoms and eliminate etiological agents. Most patients are hospitalized for complete diagnosis and observation for complications, particularly effusion and tamponade." (Braunwald E, Zipes DP, Libby P, eds. *Heart Disease: A Textbook of Cardiovascular Medicine.* 6th ed. Philadelphia: W B Saunders; 2001:1835).

Can you clarify?

See this box on our web site (www.ewjm.com) for a link to our expert's answer.